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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 08/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/068,238	BELL ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/9/04,3/22/04,5/17/04, 6/28/04*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed June 1, 2004. Claims 1-56 were previously pending, with claims 1-31 and 48-56 withdrawn from consideration. Applicants cancelled claims 1-56 and added new claims 57-96. Claims 57-96 are pending and will be examined.

2. Applicants' claim cancellations overcame the following rejections: rejection of claims 32, 35-38, 41-43, 46 and 47 under 35 U.S.C. 112, first paragraph, written description; rejection of claims 32, 36-38, 42, 43 and 47 under 35 U.S.C. 103(a) over Ramisse et al., Wittwer et al. and Qi et al.; rejection of claims 33-35 under 35 U.S.C. 103(a) over Ramisse et al., Wittwer et al. and Qi et al., and further in view of Makino et al. and Buck et al.; rejection of claims 39-41 under 35 U.S.C. 103(a) over Ramisse et al., Wittwer et al. and Qi et al., and further in view of Price et al. and Buck et al.; rejection of claims 44-46 under 35 U.S.C. 103(a) over Ramisse et al., Wittwer et al. and Qi et al., and further in view of Bragg et al. and Buck et al.

3. The art rejections applied previously to claims 32-47 will be applied to the new claims 57-96, and Applicants' arguments regarding these rejections are addressed in the "Response to Arguments" section below.

Information Disclosure Statement

4. The information disclosure statements (IDS) submitted on February 9, 2004, March 22, 2004, May 17, 2004 and June 28, 2004 were filed after the mailing date of the first office action on January 30, 2004. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Response to Arguments

5. Applicant's arguments filed June 1, 2004 have been fully considered but they are not persuasive.

A) Regarding the rejection of claims 33-35 (now equivalent to claims 57-69 and partly 96) over under 35 U.S.C. 103(a) over Ramisse et al., Wittwer et al. and Qi et al., further in view of Makino et al., Applicants argue that:

a) the claimed capB primers are not structural homologs of the sequence disclosed by Makino et al., since Makino et al. do not suggest selecting the claimed probes and primers from the sequence,

b) results of Buck et al. were not based on B. anthracis sequence, and the sequencing reaction of Buck et al. is "significantly different than, for example, PCR in which, generally two oligonucleotides are used, or real-time PCR in which, generally, at least four oligonucleotides are used",

c) the presently claimed primers and probes exhibit high sensitivity and specificity toward their targets.

Regarding a), Applicants misunderstood the rejection, which states that since Ramisse et al. teach capB primers based on the Makino et al. sequence, which was known at the time of the invention, then any other primer or probe (emphasis added) based on that sequence is a structural homolog of the primer or probe of Ramisse et al. Therefore, unless unexpected results are shown, according to Buck et al. all primers are equivalent.

Regarding b), Buck et al. provides EVIDENCE of the equivalence of primers in extension type assays, which include PCR. Applicants' arguments cannot rebut this evidentiary showing. As to the difference between PCR and sequencing, Buck et al. teach sequencing by PCR, therefore, the presence or absence of one or more primers is not relevant.

Regarding c), there is no proof in the specification that Applicants' probes and primers are more sensitive or specific than any other primer designed based on the capB sequence. In fact, the capB primers of Ramisse et al. are also specific for B. anthracis over other bacterial and Baccilus

species (see Table 1, for example). Therefore, no evidence of secondary considerations has been presented by Applicants.

Therefore, taking into account that capB primers of Ramisse et al. were specific for B. anthracis and the fact determined by Buck et al. that primers selected from the same sequence are equivalent in performance, it would have been obvious to substitute the primers of Ramisse et al. with any other primer based on the capB sequence.

B) Regarding the rejection of claims 39-41 (now equivalent to claims 70-82 and partly 96) over under 35 U.S.C. 103(a) over Ramisse et al., Wittwer et al. and Qi et al., further in view of Price et al., Applicants argue that:

a) the claimed pagA primers are not structural homologs of the sequence disclosed by Price et al., since Price et al. do not suggest selecting the claimed probes and primers from the sequence,

b) results of Buck et al. were not based on B. anthracis sequence, and the sequencing reaction of Buck et al. is "significantly different than, for example, PCR in which, generally two oligonucleotides are used, or real-time PCR in which, generally, at least four oligonucleotides are used",

c) the presently claimed primers and probes exhibit high sensitivity and specificity toward their targets.

Regarding a), Applicants misunderstood the rejection, which states that since Ramisse et al. teach pagA primers based on the Price et al. sequence, which was known at the time of the invention, then any other primer or probe (emphasis added) based on that sequence is a structural homolog of the primer or probe of Ramisse et al. Therefore, unless unexpected results are shown, according to Buck et al. all primers are equivalent.

Regarding b), Buck et al. provides EVIDENCE of the equivalence of primers in extension type assays, which include PCR. As to the difference between PCR and sequencing, Buck et al. teach sequencing by PCR, therefore, the presence or absence of one or more primers is not relevant.

Regarding c), there is no proof in the specification that Applicants' probes and primers are more sensitive or specific than any other primer designed based on the pagA sequence. In fact, the pagA primers of Ramisse et al. are also specific for B. anthracis over other bacterial and Baccilus species (see Table 1, for example). Therefore, no evidence of secondary considerations has been presented by Applicants.

Therefore, taking into account that pagA primers of Ramisse et al. were specific for B. anthracis and the fact determined by Buck et al. that primers selected from the same sequence are equivalent in performance, it would have been obvious to substitute the primers of Ramisse et al. with any other primer based on the pagA sequence.

C) Regarding the rejection of claims 44-46 (now equivalent to claims 83-95 and partly 96) over under 35 U.S.C. 103(a) over Ramisse et al., Wittwer et al. and Qi et al., further in view of Bragg et al., Applicants argue that:

a) the claimed lef primers are not structural homologs of the sequence disclosed by Bragg et al., since Bragg et al. do not suggest selecting the claimed probes and primers from the sequence,

b) results of Buck et al. were not based on B. anthracis sequence, and the sequencing reaction of Buck et al. is "significantly different than, for example, PCR in which, generally two oligonucleotides are used, or real-time PCR in which, generally, at least four oligonucleotides are used",

c) the presently claimed primers and probes exhibit high sensitivity and specificity toward their targets.

Regarding a), Applicants misunderstood the rejection, which states that since Ramisse et al. teach pagA primers based on the Bragg et al. sequence, which was known at the time of the invention, then any other primer or probe (emphasis added) based on that sequence is a structural homolog of the primer or probe of Ramisse et al. Therefore, unless unexpected results are shown, according to Buck et al. all primers are equivalent.

Regarding b), Buck et al. provides EVIDENCE of the equivalence of primers in extension type assays, which include PCR. As to the difference between PCR and sequencing, Buck et al. teach sequencing by PCR, therefore, the presence or absence of one or more primers is not relevant.

Regarding c), there is no proof in the specification that Applicants' probes and primers are more sensitive or specific than any other primer designed based on the lef sequence. In fact, the lef primers of Ramisse et al. are also specific for B. anthracis over other bacterial and Baccilus species (see Table 1, for example). Therefore, no evidence of secondary considerations has been presented by Applicants.

Therefore, taking into account that lef primers of Ramisse et al. were specific for B. anthracis and the fact determined by Buck et al. that primers selected from the same sequence are equivalent in performance, it would have been obvious to substitute the primers of Ramisse et al. with any other primer based on the lef sequence.

Claim interpretation

6. In claims 67, 68, 80, 81, 93 and 94, the limitation of a package insert having instructions for using primers and probes is not taken into account when comparing claims with the prior art, since the instructions (printed matter) do not constitute a structural limitation on primers or probes.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 57-64 and 67-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramisse et al. (FEMS Microbiology Letters, vol. 145, pp. 9-16, 1996; cited in the IDS and in the previous office action), Makino et al. (J. Bacter., vol. 171, pp. 722-730, 1989; cited in the previous office action) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999; cited in the previous office action).

A) Regarding claims 57-64 and 67-69, Ramisse et al. teach primers for detection of capB gene (Table 2). The primers were designed by computer analysis using the Oligo primer analysis software (page 12, second paragraph). Ramisse et al. do not specifically teach oligonucleotides with SEQ ID NO: 1-4.

B) As can be seen from sequence alignments, SEQ ID NO: 1 is complementary to bp 371-389 of the cap gene of Makino et al., SEQ ID NO: 2 is complementary to bp 611-628 of the cap gene of Makino et al., SEQ ID NO: 3 is complementary to bp 523-554 of the cap gene of Makino et al., and SEQ ID NO: 4 is complementary to bp 556-585 of the cap gene of Makino et al., whereas

the primers of Ramisse et al. are complementary to bp 1230-1249 and 2083-2102 of the cap gene (Table 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Ramisse et al. with the use of functionally equivalent primers selected from the sequence of Makino et al., since Ramisse et al. expressly teach primer selection for B. anthracis detection using commercially available software from the B. anthracis published sequences and since Makino et al. provide such published sequences for the software program to analyze.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

> "Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of B. anthracis, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al. expressly provides evidence of the equivalence of primers. Specifically, Buck et al. invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck et al. also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible

18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck et al. tested each of the primers selected by the methods of the different labs, Buck et al. found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck et al. expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck et al. provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

10. Claims 65 and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramisse et al. (FEMS Microbiology Letters, vol. 145, pp. 9-16, 1996; cited in the IDS; cited in the previous office action), Makino et al. (J. Bacter., vol. 171, pp. 722-730, 1989; cited in the previous office action) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999; cited in the previous office action) as applied to claims 61 and 63 above, and further in view of Wittwer et al. (Biotechniques, vol. 22, pp. 130-138, 1997; cited in the previous office action) and Qi et al. (Appl. Env. Microbiol., vol. 67, pp. 3720-3727, August 2001; cited in the previous office action).

A) Regarding claims 65 and 66, Ramisse et al. teach primers for detection of capB gene (Table 2). The primers were designed by computer analysis using the Oligo primer analysis software (page 12, second paragraph). Ramisse et al. do not specifically teach oligonucleotides comprising a donor fluorescent moiety and an acceptor fluorescent moiety.

B) Regarding claims 65 and 66, Wittwer et al. teach dual probes for detection of nucleic acids, with one part of the probe being labeled with a fluorescent donor and the other with a fluorescent acceptor (Fig. 1C; page 134, paragraphs 3 and 4; Fig. 4).

Regarding claims 65 and 66, Qi et al. teach real-time PCR detection of B. anthracis using two primers and two probes with sequences complementary to the rpoB gene. One probe is labeled with a fluorescent donor, fluoresceine, and the other with the fluorescent acceptor, Cy5 (Fig. 1; Table 3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used fluorescent labeling of probes with donor and acceptor moieties of Wittwer et al. and Qi et al. in the B. anthracis detection probes of Ramisse et al. The motivation to do so, provided by Wittwer et al., would have been that using dual probes allowed quantitation of low copy number of target nucleic acid (page 134, fourth paragraph; page 135, the end of first paragraph) and

"Fluorescence monitoring every cycle during DNA amplification is an extraordinarily powerful technique for quantification. With simple instrumentation and fluorescent monitoring each cycle, sequence-specific detection and quantification can be achieved in 5–20 min after temperature cycling has begun. Although the final fluorescence signal is decreased when low copy numbers are amplified, quantification between 0 and 1000 initial template copies appears possible (Figures 3 and 4). These techniques should be particularly useful in assays where rapid quantification is desired, such as in the amplification of clinical serum viruses." (page 138, last paragraph).

Further, the motivation to do so, provided by Qi et al., would have been that using FRET-based detection allowed detection of B. anthracis, a potential biological weapon, in less than an hour (Abstract), could detect as little as 1pg of DNA (page 3726, second paragraph), and

"The FRET-PCR assay has several advantages over standard molecular identification techniques. The amplification is monitored in real time, and reactions can be scored as positive or negative without time-consuming routine gel analysis. Moreover, the assay is rapid and highly sensitive when extracted DNA is used as a template for PCR. ... The presence of contaminating DNA does not affect the results of the assay, and hence it can be applied for detection of *B. anthracis* in epidemiological studies and suspected bioterrorist attacks and when analyzing ancient samples." (page 3726, last paragraph; page 3727, first paragraph).

11. Claims 70-77 and 80-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramisse et al. (FEMS Microbiology Letters, vol. 145, pp. 9-16, 1996; cited in the IDS; cited in the previous office action), Price et al. (J. Bacter., vol. 181, pp. 2358-2362, 1999; cited in the previous office action) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999 ; cited in the previous office action).

A) Regarding claims 70-77 and 80-82, Ramisse et al. teach primers for detection of pagA gene (Table 2). The primers were designed by computer analysis using the Oligo primer analysis software (page 12, second paragraph). Ramisse et al. do not specifically teach oligonucleotides with SEQ ID NO: 5-8.

B) As can be seen from sequence alignments, SEQ ID NO: 5 is complementary to bp 852-870 of the pagA gene of Price et al., SEQ ID NO: 6 is complementary to bp 1163-1180 of the pagA gene of Price et al., SEQ ID NO: 7 is complementary to bp 1041-1062 of the pagA gene of Price et al., and SEQ ID NO: 4 is complementary to bp 1064-1086 of the pagA gene of Price et al., whereas the primers of Ramisse et al. are complementary to bp 1925-1944, 2652-2671, 2006-2027 and 2135-2156 of the pagA gene (Table 2). Further, Price et al. teach primers for amplification of pagA gene (Table 1), which were designed from published pag sequence (page 2358, sixth paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Ramisse et al. with the use of functionally equivalent primers selected from the sequence of Price et al., since Ramisse et al. expressly teach primer selection using commercially available software for B. anthracis detection from the B. anthracis published sequences and since Price et al. provide such published sequences for the software program to analyze, and also teach primers for amplification of pagA.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

> "Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of B. anthracis, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al. expressly provides evidence of the equivalence of primers. Specifically, Buck et al. invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck et al. also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck et al. tested each of the primers selected by the methods of the different labs, Buck et al. found that EVERY

SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck et al. expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck et al. provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

12. Claims 78 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramisse et al. (FEMS Microbiology Letters, vol. 145, pp. 9-16, 1996; cited in the IDS; cited in the previous office action), Price et al. (J. Bacter., vol. 181, pp. 2358-2362, 1999; cited in the previous office action) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999 ; cited in the previous office action), as applied to claims 74 and 76 above, and further in view of Wittwer et al. (Biotechniques, vol. 22, pp. 130-138, 1997; cited in the previous office action) and Qi et al. (Appl. Env. Microbiol., vol. 67, pp. 3720-3727, August 2001; cited in the previous office action).

A) Regarding claims 78 and 79, Ramisse et al. teach primers for detection of pagA gene (Table 2). The primers were designed by computer analysis using the Oligo primer analysis software (page 12, second paragraph). Ramisse et al. do not specifically teach oligonucleotides comprising a donor fluorescent moiety and an acceptor fluorescent moiety.

B) Regarding claims 78 and 79, Wittwer et al. teach dual probes for detection of nucleic acids, with one part of the probe being labeled with a fluorescent donor and the other with a fluorescent acceptor (Fig. 1C; page 134, paragraphs 3 and 4; Fig. 4).

Regarding claims 78 and 79, Qi et al. teach real-time PCR detection of B. anthracis using two primers and two probes with sequences complementary to the rpoB gene. One probe is labeled with a fluorescent donor, fluoresceine, and the other with the fluorescent acceptor, Cy5 (Fig. 1; Table 3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used fluorescent labeling of probes with donor and acceptor moieties of Wittwer et al. and Qi et al. in the B. anthracis detection probes of Ramisse et al. The motivation to do so, provided by Wittwer et al., would have been that using dual probes allowed quantitation of low copy number of target nucleic acid (page 134, fourth paragraph; page 135, the end of first paragraph) and

"Fluorescence monitoring every cycle during DNA amplification is an extraordinarily powerful technique for quantification. With simple instrumentation and fluorescent monitoring each cycle, sequence-specific detection and quantification can be achieved in 5–20 min after temperature cycling has begun. Although the final fluorescence signal is decreased when low copy numbers are amplified, quantification between 0 and 1000 initial template copies appears possible (Figures 3 and 4). These techniques should be particularly useful in assays where rapid quantification is desired, such as in the amplification of clinical serum viruses." (page 138, last paragraph).

Further, the motivation to do so, provided by Qi et al., would have been that using FRET-based detection allowed detection of B. anthracis, a potential biological weapon, in less than an hour (Abstract), could detect as little as 1pg of DNA (page 3726, second paragraph), and "The FRET-PCR assay has several advantages over standard molecular identification techniques. The amplification is monitored in real time, and reactions can be scored as positive or negative without time-consuming routine gel analysis. Moreover, the assay is rapid and highly sensitive when extracted DNA is used as a template for PCR. … The presence of contaminating DNA does

not affect the results of the assay, and hence it can be applied for detection of *B. anthracis* in epidemiological studies and suspected bioterrorist attacks and when analyzing ancient samples." (page 3726, last paragraph; page 3727, first paragraph).

13. Claims 83-90 and 93-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramisse et al. (FEMS Microbiology Letters, vol. 145, pp. 9-16, 1996; cited in the IDS; cited in the previous office action), Bragg et al. (Gene, vol. 81, pp. 45-54, 1989; cited in the previous office action) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999; cited in the previous office action).

A) Regarding claims 83-90 and 93-95, Ramisse et al. teach primers for detection of lef gene (Table 2). The primers were designed by computer analysis using the Oligo primer analysis software (page 12, second paragraph). Ramisse et al. do not specifically teach oligonucleotides with SEQ ID NO: 9-12.

B) As can be seen from sequence alignments, SEQ ID NO: 9 is complementary to bp 2469-2488 of the lef gene of Bragg et al., SEQ ID NO: 10 is complementary to bp 2791-2807 of the lef gene of Bragg et al., SEQ ID NO: 11 is complementary to bp 2607-2628 of the lef gene of Bragg et al., and SEQ ID NO: 12 is complementary to bp 2631-2652 of the lef gene of Bragg et al., whereas the primers of Ramisse et al. are complementary to bp 949-970, 1921-1941, 1238-1258 and 1599-1622 of the lef gene (Table 2). Further, Bragg et al. teach primers for sequencing of lef gene, which span the entire sequence of the gene (page 46, sixth paragraph; Fig. 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Ramisse et al. with the use of functionally equivalent primers selected from the sequence of Bragg et al., since Ramisse et al. expressly teach primer selection using commercially available software for B. anthracis detection from the B. anthracis published sequences and since Bragg et al. provide such published sequences for the software

program to analyze. Further, Bragg et al. teach primers spanning the entire sequence of the lef gene.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

> "Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of B. anthracis, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al. expressly provides evidence of the equivalence of primers. Specifically, Buck et al. invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck et al. also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck et al. tested each of the primers selected by the methods of the different labs, Buck et al. found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck et al. expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck et al. provides direct evidence that all primers

would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

14. Claims 91 and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramisse et al. (FEMS Microbiology Letters, vol. 145, pp. 9-16, 1996; cited in the IDS; cited in the previous office action), Bragg et al. (Gene, vol. 81, pp. 45-54, 1989; cited in the previous office action) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999; cited in the previous office action), as applied to claims 87 and 89 above, and further in view of Wittwer et al. (Biotechniques, vol. 22, pp. 130-138, 1997 ; cited in the previous office action) and Qi et al. (Appl. Env. Microbiol., vol. 67, pp. 3720-3727, August 2001; cited in the previous office action).

A) Regarding claims 91 and 92, Ramisse et al. teach primers for detection of lef gene (Table 2). The primers were designed by computer analysis using the Oligo primer analysis software (page 12, second paragraph). Ramisse et al. do not specifically teach oligonucleotides comprising a donor fluorescent moiety and an acceptor fluorescent moiety.

B) Regarding claims 91 and 92, Wittwer et al. teach dual probes for detection of nucleic acids, with one part of the probe being labeled with a fluorescent donor and the other with a fluorescent acceptor (Fig. 1C; page 134, paragraphs 3 and 4; Fig. 4).

Regarding claims 91 and 92, Qi et al. teach real-time PCR detection of B. anthracis using two primers and two probes with sequences complementary to the rpoB gene. One probe is labeled with a fluorescent donor, fluoresceine, and the other with the fluorescent acceptor, Cy5 (Fig. 1; Table 3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used fluorescent labeling of probes with donor and acceptor moieties of Wittwer et al. and Qi et al. in the B. anthracis detection probes of Ramisse et al. The motivation to do so, provided by Wittwer et al., would have been that using dual probes allowed quantitation of low copy number of target nucleic acid (page 134, fourth paragraph; page 135, the end of first paragraph) and

"Fluorescence monitoring every cycle during DNA amplification is an extraordinarily powerful technique for quantification. With simple instrumentation and fluorescent monitoring each cycle, sequence-specific detection and quantification can be achieved in 5–20 min after temperature cycling has begun. Although the final fluorescence signal is decreased when low copy numbers are amplified, quantification between 0 and 1000 initial template copies appears possible (Figures 3 and 4). These techniques should be particularly useful in assays where rapid quantification is desired, such as in the amplification of clinical serum viruses." (page 138, last paragraph).

Further, the motivation to do so, provided by Qi et al., would have been that using FRET-based detection allowed detection of B. anthracis, a potential biological weapon, in less than an hour (Abstract), could detect as little as 1pg of DNA (page 3726, second paragraph), and "The FRET-PCR assay has several advantages over standard molecular identification techniques. The amplification is monitored in real time, and reactions can be scored as positive or negative without time-consuming routine gel analysis. Moreover, the assay is rapid and highly sensitive when extracted DNA is used as a template for PCR. ... The presence of contaminating DNA does not affect the results of the assay, and hence it can be applied for detection of *B. anthracis* in epidemiological studies and suspected bioterrorist attacks and when analyzing ancient samples." (page 3726, last paragraph; page 3727, first paragraph).

15. Claim 96 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ramisse et al. (FEMS Microbiology Letters, vol. 145, pp. 9-16, 1996; cited in the IDS; cited in the previous office action), Makino et al. (J. Bacter., vol. 171, pp. 722-730, 1989; cited in the previous office action), Price et al. (J. Bacter., vol. 181, pp. 2358-2362, 1999; cited in the previous office action), Bragg et al. (Gene, vol. 81, pp. 45-54, 1989; cited in the previous office action) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999 ; cited in the previous office action).

A) Regarding claim 96, Ramisse et al. teach primers for detection of capB gene, pag A gene and lef gene (Table 2). The primers were designed by computer analysis using the Oligo primer analysis software (page 12, second paragraph). Ramisse et al. do not specifically teach oligonucleotides with SEQ ID NO: 1-12.

B) As can be seen from sequence alignments, SEQ ID NO: 1 is complementary to bp 371-389 of the cap gene of Makino et al., SEQ ID NO: 2 is complementary to bp 611-628 of the cap gene of Makino et al., SEQ ID NO: 3 is complementary to bp 523-554 of the cap gene of Makino et al., and SEQ ID NO: 4 is complementary to bp 556-585 of the cap gene of Makino et al., whereas the primers of Ramisse et al. are complementary to bp 1230-1249 and 2083-2102 of the cap gene (Table 2).

C) As can be seen from sequence alignments, SEQ ID NO: 5 is complementary to bp 852-870 of the pagA gene of Price et al., SEQ ID NO: 6 is complementary to bp 1163-1180 of the pagA gene of Price et al., SEQ ID NO: 7 is complementary to bp 1041-1062 of the pagA gene of Price et al., and SEQ ID NO: 4 is complementary to bp 1064-1086 of the pagA gene of Price et al., whereas the primers of Ramisse et al. are complementary to bp 1925-1944, 2652-2671, 2006-2027 and 2135-2156 of the pagA gene (Table 2). Further, Price et al. teach primers for amplification of pagA gene (Table 1), which were designed from published pagA sequence (page 2358, sixth paragraph).

D) As can be seen from sequence alignments, SEQ ID NO: 9 is complementary to bp 2469-2488 of the lef gene of Bragg et al., SEQ ID NO: 10 is complementary to bp 2791-2807 of the lef gene of Bragg et al., SEQ ID NO: 11 is complementary to bp 2607-2628 of the lef gene of Bragg et al., and SEQ ID NO: 12 is complementary to bp 2631-2652 of the lef gene of Bragg et al., whereas the primers of Ramisse et al. are complementary to bp 949-970, 1921-1941, 1238-1258 and 1599-1622 of the lef gene (Table 2). Further, Bragg et al. teach primers for sequencing of lef gene spanning the entire length of the gene (page 46, sixth paragraph; Fig. 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Ramisse et al. with the use of functionally equivalent primers selected from the sequences of Makino et al., Price et al. and Bragg et al., since Ramisse et al. expressly teach primer selection using commercially available software for B. anthracis detection from the B. anthracis published sequences and since Makino et al., Price et al. and Bragg et al. provide such published sequences for the software program to analyze.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

> "Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of B. anthracis, and concerning which a biochemist of ordinary skill would attempt to obtain alternate

compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

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16. No claims are allowed.

Conclusion

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the

THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TS

August 10, 2004

JEFFREY FREDMAN
PRIMARY EXAMINER
8/11/04